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# RECENT ADVANCES IN THE MEDICAL TREATMENT OF ESSENTIAL HYPERTENSION WITH PARTICULAR REFERENCE TO DRUGS

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There is no disease for which specific therapy is more urgently needed than essential hypertension. Statisticians estimate that half of the population over the age of 40 will die of hypertension or its complications, and that there are 15,000,000 people with hypertension in the United States today. Results with surgical sympathectomy, and with special diets in the treatment of hypertension have demonstrated that the blood pressure may be lowered in certain patients without harmful effects and, indeed, with apparent benefit. In such cases it seems obvious that elevation of the blood pressure fulfills no necessary function and should be corrected, provided it can be done by benign methods. This paper summarizes the experience in this clinic with the pharmacological treatment of hypertension with particular reference to new hypotensive agents.

## GENERAL CONSIDERATIONS

Not all hypertensive patients require treatment directed at reducing the blood pressure. In mild cases a conservative approach utilizing psychotherapy, sedation, reassurance, and a regimen of living designed to ease the customary tensions of life probably is the treatment of choice. This conclusion is supported by the observation that certain patients, particularly females, may live out a normal life span without treatment of any kind. Nevertheless statistics derived from large series such as those of insurance companies definitely prove that in general hypertension shortens life. Therefore, a prime consideration in determining therapy for a given patient is to assess his prognosis without treatment.

**Prognostic Signs.**—The most significant of the prognostic signs are as follows:

1. *The Level of Blood Pressure.*—An elevation of diastolic pressure above 120 mm. of mercury usually indicates a poor prognosis. The level of systolic pressure must be interpreted with certain reservations. For example, elderly individuals whose larger arteries have lost their elasticity may exhibit systolic pressures out of proportion to the diastolic

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levels, whereas young nervous patients under emotional stress may have temporary systolic without diastolic elevations. As a general rule, however, as systolic pressure rises over 200 mm. of mercury it warrants a progressively graver prognosis.

2. *The Lability of the Blood Pressure.*—Experience has shown that hypertensive patients whose blood pressures fall markedly after a period of rest in bed generally have a more benign form of the disease and respond more readily to conservative medical treatment than patients whose blood pressures are fixed. Similarly, a marked hypotensive response to sodium amytal "narcosis," as a rule, denotes a better prognosis than a slight or negative response to this test.

3. *The Optic Fundi and the Kidneys.*—The development of neuroretinitis with papilledema indicates a malignant transition; it is almost always associated with increased levels of diastolic pressure and signs of renal impairment such as the presence of albumin, red cells and/or casts in the urine, impairment of ability to concentrate the urine and excrete phenolsulfonphthalein normally. When these signs develop death occurs usually in less than one year in untreated patients. If the optic fundi are examined frequently the diagnosis of a malignant change may be made before the disease has progressed to an irreversible stage; and life may be prolonged considerably by sympathectomy, dietotherapy, or drug treatment either alone or preferably in combination.

4. *The Cardiac Status.*—Enlargement of the heart by physical signs and roentgenography, decreasing exercise tolerance, paroxysmal nocturnal dyspnea, the appearance of an aortic-diastolic murmur, gallop rhythm or pulsus alternans all indicate imminent or obvious cardiac failure. These signs and symptoms may respond to digitalis for a time, but as a rule they require, in addition, rigid sodium restriction and hypotensive drugs.

Such tests as the cold and postural test, the sedation test, renal function tests, examination of the heart and fundi are at best prognostic guides, and also may be of value in selecting patients for surgical sympathectomy. However, these tests are of little use in deciding which type of therapeutic procedure, diet, surgery, or drugs will produce the greatest reduction of blood pressure and relief of symptoms in the individual case. As yet, there are no tests other than a therapeutic trial to determine the most effective hypotensive procedure.

## CRITERIA FOR EFFECTIVENESS OF HYPOTENSIVE DRUGS

During the past several years in this clinic the effects of a variety of drugs have been investigated in hypertensive patients. In this study the following therapeutic criteria have been used to assess the relative effectiveness of these agents.

1. The first requirement of a therapeutic agent for hypertension is that it should lower the blood pressure significantly in a fair proportion of patients. A host of drugs and nostrums have been used in the past, with no proven hypotensive effect in most cases. Controlled studies have demonstrated that such substances as extracts of onion, mistletoe, garlic and watermelon seed, the organic nitrates and the xanthines do not lower the blood pressure significantly in the doses customarily advised.

2. The hypotensive effect should be accomplished without serious detriment to the patient. For example, certain procedures such as the administration of pyrogenic substances, bleeding to the point of collapse, or starvation, cannot be considered therapeutic even though they lower blood pressure. Likewise certain pharmacological agents such as pentaquine, while effective in lowering blood pressure, are too toxic for clinical use.

3. Accompanying the hypotensive response there should be definite clinical indications of arrest or preferably reversal of the disease, such as symptomatic relief, a reduction in the cardiac size, clearing of neuroretinitis and/or other evidences of general improvement.

4. The drug should have a duration of action of at least eight hours, otherwise the necessity for frequent dosage interferes with the patient's normal habits of life, particularly with his sleep. Examples of drugs whose duration of action is too brief to be of value in long-term treatment are sodium nitrite and tetraethylammonium salts.

5. Finally, a satisfactory agent should be effective by mouth or at least by subcutaneous injection. An agent such as dibenamine, that must be administered in a dilute solution by slow intravenous drip, is not practical for long-term treatment.

With these criteria in mind it seems worthwhile to review the more useful of the medical procedures that have been applied in the treatment of essential hypertension.

## POTASSIUM THIOCYANATE

The therapeutic effectiveness of the thiocyanates in essential hypertension has been a controversial point. Experience in this clinic has demonstrated a significant reduction of blood pressure in somewhat less than 10 per cent of patients treated. In these few cases, however, the response has been quite favorable with freedom from toxic effects, and relief of symptoms. In some patients there has been relief of symptoms, particularly headache and emotional irritability, without a demonstrable lowering of blood pressure, while in others there has been aggravation of symptoms.

As a result of these experiences the use of thiocyanate in this clinic is now restricted to the few patients who after a trial period of several months have exhibited a definite hypotensive effect. If the blood pressure is not significantly reduced after such a trial the drug is withdrawn and some other form of treatment substituted. Before beginning treatment it is important to evaluate the efficiency of the kidneys by means of the history and such laboratory procedures as the routine urinalysis, the concentration-dilution test, the phenolsulfonphthalein test and the blood nonprotein nitrogen concentration, since patients with renal impairment may develop high serum levels of thiocyanate on relatively low dosage.

Because the thiocyanates are potentially highly toxic substances when the level in the blood exceeds 10 to 12 mg. per 100 cc. it is imperative that the physician using this agent have at his disposal some means of making frequent determinations of the blood thiocyanate concentration. It is well also to keep in mind the type of toxic reactions that may be encountered, since fatalities have occurred with careless administration.

The severe reactions are psychosis and exfoliative dermatitis. Severe toxic psychosis is the most dangerous of the toxic symptoms as it precedes the majority of deaths. The clinical state may be characterized by dysarthria, mental dullness, aphasia, delirium, clonic contractures and hallucinations. In fatal cases, despite discontinuation of the drug, there is a progressive downhill course with stupor, convulsions, sphincter incontinence, collapse and death. The majority of such fatalities have occurred in patients whose blood levels were not carefully controlled.

Less severe toxic manifestations such as gastrointestinal disorders including diarrhea, nausea and vomiting, and abdominal pain are seldom observed unless the blood level rises above 12 mg. per 100 cc. Various types of dermatitis including exanthematous, acneiform, or iodotic rash, furunculosis and purpura may occur but disappear soon after discontinuation of treatment.

Thyroid enlargement, mild myxedema and even goitre may appear during thiocyanate administration, an effect produced by thiocyanate blockade of the formation of thyroxin in the thyroid gland. The block may be overcome by administration of an excess of iodine in the form of a saturated solution of potassium iodide (10 drops three times per day in water). General weakness and fatigue occurs in more than half the cases but tends to disappear after several weeks or months of continued treatment.

Treatment with potassium thiocyanate is begun by the administra-

tion of 0.06 gm. (1 grain) in enteric coated tablets * three times per day before or after meals. The blood level must be determined at least once each week and is used as a guide in adjusting dosage. Dosage is increased by 0.06 to 0.12 gm. (1 to 2 grains) at weekly intervals until the serum concentration reaches 8 to 12 mg. per 100 cc. and is maintained at this level for at least three weeks, with weekly checks of the blood pressure and serum concentration of thiocyanate.

If no hypotensive response occurs at the end of three to four weeks the drug is withdrawn. However, if there is a definite reduction in blood pressure or marked symptomatic improvement dosage is gradually adjusted downward. The reason for thus reducing the dosage is that many patients who respond to thiocyanates will have as good a therapeutic effect and not as much toxicity with blood levels between 4 and 8 mg. per 100 cc. as they will with levels between 8 and 12 mg. per 100 cc. After final adjustment of dosage the patient may be seen at intervals of approximately one month when the blood levels always should be determined.

It is impossible to predict the dosage required by any patient from his surface area or other available criteria; the dose required to maintain a therapeutic blood level varies from 0.2 to 0.6 gm. of potassium thiocyanate daily. Therefore, under no circumstances may thiocyanate be administered unless there are laboratory facilities available for determining the serum levels of the drug.

### SYMPATHOLYTIC AGENTS

Surgical sympathectomy in the treatment of essential hypertension has stimulated great interest in chemical agents which will block sympathetically innervated vasoconstriction. Several blocking agents have been produced, but for various reasons few of these are practical in the long term clinical treatment of patients.

Examples of sympatholytic agents studied in hypertensive patients in this clinic are tetraethylammonium salts, dibenamine, pentaquine, and the dihydrogenated derivatives of ergotoxine. These agents have certain pharmacologic effects in common: they all may produce a fall of blood pressure, particularly in the erect position, but the duration and the degree of the fall are extremely variable in different patients, and are not related directly either to dosage or to the completeness of sympathetic blockade. Other evidences of sympatholysis, including nasal stuffiness, inhibition of reflex sympathetic vasoconstriction in the fingers and toes, and depression of vasopressor responses may also vary greatly in different patients.

* Supplied by the Eli Lilly Company.

The duration of the sympatholytic action varies with the drug used, tetraethylammonium being the shortest, the dihydrogenated derivatives and dibenamine intermediate, and pentaquine the longest acting. Pharmacologically these drugs are of interest because they block the sympathetic nervous system at different sites.

*Tetraethylammonium bromide* or *chloride* (Etamon *) is effective only by parenteral administration. The dose of Etamon administered intravenously is 0.2 to 0.3 gm. Although the drug has been used therapeutically in peripheral vascular disease, especially in angiospastic conditions of the extremities such as Raynaud's disease and thromboangiitis obliterans, the duration of the hypotensive response is too brief to be of value in treating hypertensive patients. Further, because there is also parasympathetic blockade, the hypotensive response is accompanied by tachycardia and palpitation, particularly in the erect position. There is usually some paralysis of visual accommodation.

*Dibenamine* (dibenzyl-bis-chloro-ethyl-amine) is said to block sympathetic impulses peripherally at the effector cells. Being a nitrogen mustard derivative it is too caustic to be administered by any other route than intravenously in dilute solution by constant slow drip. The dose of 5 mg. per kg. is diluted in 500 cc. of saline administered over a period of an hour. Despite meticulous technic patients may develop chemical thromboses at the sites of administration. In animals the drug blocks or inhibits both excitatory sympathetic nervous functions and the effects of epinephrine. In man in therapeutic doses an adrenolytic effect has seldom been observed, but its sympatholytic effects, including hypotension, may last from several hours to several days. Visual accommodation is impaired and in some female patients we have noted temporary loss of voluntary bladder control in the erect position.

*Pentaquine,* a synthetic derivative of plasmochin, was developed during the war for the treatment of malaria. It was noted that when the drug was administered to both normal individuals and malarial patients postural hypotension occasionally developed and persisted for several weeks or longer. In animals it was found that both pentaquine and plasmochin block sympathetic reflexes in the central nervous system rather than at the ganglia or peripherally. In hypertensive patients, including those in the malignant phase of essential hypertension, there was a variable but often striking reduction of blood pressure after several days of oral administration. Such large doses were required that many patients developed toxic effects including abdominal pains, weakness, anorexia and methemoglobinemia. Visual accommodation was not

* Parke, Davis and Company.

impaired. The postural hypotension which lasted several days to several weeks following discontinuation of the drug differed from that observed with tetraethylammonium and dibenamine in that it was not accompanied by significant increase in pulse rate. Several patients with advanced malignant hypertension were treated and it is significant that despite continued hypotension their nitrogen retention gradually increased and they eventually died in uremia.

The *dihydrogenated alkaloids of the ergotoxine group* like pentaquine are believed to produce a central blockade of sympathetic reflexes. To date the most useful hypotensive agent in this group of three compounds has been dihydroergocornine (DHO 180). It was effective by any route, the intravenous dose being approximately 0.25 mg. and the oral dose 2 to 8 mg. administered prior to breakfast. In reactive patients the hypotensive effect lasted eight hours to several days. The drug was remarkably free of toxic side effects particularly when administered orally. Transient nasal stuffiness was the only side effect noted following oral administration.

Postural collapse from DHO 180 could be avoided in most patients by reducing the dosage or by fitting the patient with an abdominal binder and elastic stockings. Nausea and vomiting occurred occasionally after intravenous administration. Although supplies of this agent are still limited to investigational work it would appear at present to be the most promising of the sympatholytic agents for use in treating hypertensive patients. However, final evaluation of this drug must await further clinical studies.

It is by no means certain that any sympatholytic drug will provide a solution to the problem of treating the majority of hypertensive patients. Unfortunately not all patients react to these drugs with a fall in blood pressure. Despite complete abolition of sympathetic vasomotor reflexes some patients fail to exhibit significant hypotension, suggesting that in these individuals mechanisms other than an overactive sympathetic nervous system are involved in maintaining the hypertension. Further, the sympatholytic agents that act peripherally produce disturbances in visual accommodation, while all of them cause postural hypotension and moderate debility as concerns sudden physical effort. Finally, this whole approach to the problem of hypertension is so recent that little should be concluded as to its ultimate value.

### VERATRUM VIRIDE

Of all the drugs used in this clinic to lower blood pressure in essential hypertension, veratrum viride has produced the most marked reduction of blood pressure in the greatest number of patients. Recent

studies of its clinical and pharmacological effects indicate that the hypotensive action may occur in subtoxic dosage, and that there are no harmful effects on the heart or kidneys following acute or chronic administration.

The veratrum alkaloids have been condemned in pharmacologic textbooks because they were thought to be cardiac depressants, and because they were misused in the past to "soften the pulse" and lower the body temperature in febrile illnesses. However, more recent pharmacologic investigations in animals and in hypertensive patients have demonstrated that the fall in blood pressure which occurs after therapeutic doses of the drug is due to a decrease in peripheral resistance rather than to a depression of cardiac output. As the blood pressure falls the blood flow through the liver, the kidney and the extremities at first decreases slightly, but then returns to or even above the previous levels despite a continued reduction of blood pressure. From animal experiments it is known that the veratrum alkaloids stimulate the afferent vagal nerve endings in the thorax and particularly in the myocardium of the left ventricle from which nervous discharges travel to the brain and initiate a reflex fall in blood pressure and usually in pulse rate. The slowing of cardiac rate presumably is due to stimulation of the efferent vagus because it may be abolished by atropine; but the other efferent pathways which cause the hypotension are not known. Studies have shown that the sympathetic reflexes are not blocked and that the cholinergic vasodilator nerves are probably not stimulated since atropine does not abolish the hypotension.

Clinically veratrum viride may be administered parenterally (Veratrone *) or orally (Vertavis †). The oral preparation seems preferable because it is more readily administered and its hypotensive effect is of longer duration. Vertavis tablets contain the whole dry powdered veratrum viride biologically standardized so that each tablet contains 10 Craw units. Following an effective oral dose of the drug the hypotensive effect usually begins in one to two hours, reaches a maximum in four to six hours, and ends in ten to fourteen hours. Therefore, in order to avoid cumulative overdosage it is usually expedient to administer the drug at eight to twelve hour intervals.

Successful treatment with veratrum requires meticulous attention to dosage because of the nausea and vomiting that may occur, particularly during long-term administration. These undesirable side effects may appear with doses only slightly greater than the therapeutic dose, and in some patients with doses insufficient to produce a hypotensive effect.

* Parke, Davis and Company.
† Irwin, Neisler and Company.

However, in most patients successful therapeutic results can be achieved by proper spacing of dosage.

There is a great variability from patient to patient in the amount of veratrum required to produce a hypotensive response. Therefore, in hospitalized patients the effective dose must be determined in each instance by administering one tablet of Vertavis (10 Craw units) every two hours until a therapeutic or toxic effect results. Having found the level to which the patient responds this dose is administered at twelve hour intervals morning and night. Vomiting is less often encountered if each twelve hour dosage period is further subdivided so that no more than 10 Craw units are administered each hour.

In ambulatory patients, dosage is begun by instructing the patient to take one tablet (10 Craw units) before breakfast and before the evening meal. The patient is seen the next week approximately four to six hours after the morning dose and his blood pressure is taken. If no hypotensive effect is observed and there have been no toxic reactions, the dose is increased to 10 Craw units before breakfast and one hour later after breakfast, before supper and one hour later after supper (four tablets per day). In this way the amount of the drug is increased by one or two tablets a day at weekly intervals until the effective and/or toxic dose has been determined. Occasionally patients may require readjustment of dosage either upward or downward after weeks or months of continuous treatment.

The hypotensive response to long-continued administration is seldom as dramatic as that seen after short term administration. For this reason results have been especially favorable in the treatment of hypertensive encephalopathy when the drug was administered in doses of 10 Craw units every hour or two until the blood pressure was reduced. However, long-continued treatment resulted in a significant reduction of blood pressure in about one third of the patients treated when dosage was carefully readjusted as the need arose. The hypotensive response was usually accompanied by symptomatic relief of exertional dyspnea, palpitation, nervous irritability and headache. Attacks of angina pectoris in some cases became less frequent but in others did not change. More objective signs of improvement were evidenced by a diminution in cardiac size, occasional reversal of the left ventricular strain patterns in the electrocardiogram and clearing of hemorrhages and exudates in the optic fundi. Patients manifesting albuminuria and a decreased excretion of phenolsulfonphthalein continued to exhibit these signs of renal impairment despite other evidences of improvement. Thus, clinically improvement was evidenced in the heart and optic fundi but not in the previously damaged kidney.

As already mentioned the principal side effect of veratrum viride was the development of nausea and vomiting, often accompanied by a sense of tightness in the throat, excessive salivation and occasionally by paresthesias about the mouth, jaw, hands and feet. Rarely there was a transient blurring of vision which was apparently unrelated to paralysis of visual accommodation. All these effects disappeared within a few hours after discontinuing the drug.

If too large a dose was given at one time or if doses were given at too frequent intervals a cumulative effect occurred, with a profound reduction in blood pressure, and collapse in the upright position associated with severe vomiting and marked bradycardia. The bradycardia and to some extent the vomiting could be abolished by doses of 1 mg. (1/60th grain) of atropine intravenously or intramuscularly and the hypotension by ephedrine (0.05 gm. intramuscularly). Such marked hypotension and bradycardia, which conceivably might predispose toward cerebral or coronary artery thrombosis, especially in arteriosclerotic patients, should be avoided by careful attention to the methods of adjusting dosage outlined above.

About 10 to 20 per cent of the patients failed to exhibit a hypotensive response to subtoxic doses of veratrum viride and in these patients treatment with this drug had to be abandoned. In another small percentage the addition of half the morning or evening dose at 2:00 P.M. was necessary to continue the hypotension because the hypotensive effect was maintained for no more than six hours following administration of the drug. It is evident, therefore, that because of two factors, the great variability of the effective dose in different patients, and the narrow margin between the therapeutic and toxic doses, treatment with this agent requires considerable attention and persistence on the part of the physician.

## DIETOTHERAPY

Although this paper is concerned primarily with drug therapy, recent advances in dietotherapy merit additional comment. The Kempner rice diet has been difficult to administer in this clinic over long periods principally because of the unpalatability and monotony of the diet and also because of the weight loss and weakness encountered in some patients. Further, experience so far fails to indicate that the rice diet provides a greater reduction in blood pressure or more symptomatic relief than a salt-free diet as advocated by Allen many years ago.

Most of the so-called "salt-free" diets advocated in the past have not provided sufficient restriction of sodium. The sodium content of the daily ration should be reduced to below 0.5 gm. for satisfactory results.

The preparation of such diets may be aided by substituting salt-free milk powder (Lanolac *) and salt-free bread. The Mead Johnson Company recently have conducted sodium analyses of commonly used American foodstuffs. A list of the sodium content of these foods and the menus of diets poor in sodium may be obtained from the research department of this company. The flat taste of food prepared without salt may be counteracted to some extent by the use of a salt-substitute, the principle ingredient of which is potassium chloride (Neocurtasal †). In addition, since there is no evidence that caffeine aggravates hypertension, patients are allowed to flavor the salt-free milk powder with coffee, tea, or cocoa. Meat and fresh fish in small amounts and almost all vegetables are permitted. These modifications permit a palatable, varied and nutritious diet which is sufficiently low in sodium content. Additional salt deprivation may be obtained by administering a mercurial diuretic once or twice per week.

Approximately half of the patients maintained on either the Kempner rice diet or the salt-poor diet manifested a significant reduction in blood pressure after several weeks. All patients with hypertension complicated by cardiac failure are benefited by sodium restriction and mercurial diuretics regardless of any hypotensive effect. Certain patients with far advanced hypertensive disease and renal failure responded poorly, probably because of the excessive amounts of sodium which these patients customarily lose in the urine. In such patients it is possible to produce collapse and increased nitrogen retention through strict restriction of sodium.

## COMBINED THERAPY

Drugs and dietotherapy in combination often may be used to advantage. Thus, patients who exhibit only slight to moderate hypotensive responses with either adequate salt restriction or veratrum viride alone, may be definitely benefited by the combination of both types of treatment. Likewise either or both treatments may be more effective after, as compared with before, lumbodorsal splanchnicectomy. Similarly, dihydroergocornine in reactive patients has enhanced the hypotensive effects of either the salt-poor diet or veratrum, or both.

In addition to these more or less specific measures, the treatment of the personality of the patient in relation to his environment plays an important part in the well-managed case. A sympathetic and hopeful attitude, the willingness to listen to the patient's personal problems,

* Mead Johnson Company.
† Winthrop.

the prescribing of rest periods and the wise use of occupational therapy provide additional supports to a well-rounded plan of therapy.

In conclusion, it is apparent that as yet no single method of treatment will produce a satisfactory reduction of blood pressure in every patient with essential hypertension. However, the recent additions of sympathectomy, dietotherapy and effective hypotensive drugs such as veratrum viride and dihydroergocornine to our armamentarium has provided the beginnings of a more positive therapeutic approach to the disease. The ultimate value of these newer therapeutic procedures must await the test of time.